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EDITORIAL

Interventional psychiatry: the revolution has arrived

Charles R. **Conway**,[1] Harold A. **Sackeim**[2,3]

[1]*School of Medicine, Department of Psychiatry, Washington University, St. Louis, MO, USA.* [2]*Department of Psychiatry, Columbia University, New York, NY, USA.* [3]*Department of Radiology, Columbia University, New York, NY, USA.*

With the exception of electroconvulsive therapy (ECT), for the past 100 years, psychiatric illnesses have been treated primarily with pharmacotherapy and psychotherapy. While these therapeutic strategies are effective for many patients with major depression, anxiety, psychosis, and other psychiatric disorders, a significant percentage do not meaningfully benefit. The profound clinical need engendered by treatment resistance and technological advances in the field of neuromodulation have led to a revolution in psychiatric care and the emergence of Interventional Psychiatry as a new subspecialty. Interventional Psychiatry pertains to the conduct of procedures involving the administration of electrical or other forms of focused energy (e.g., magnetic, sonic) to alter brain network function in a manner that ameliorates symptoms.[1] The brain stimulation interventions now in routine clinical use include ECT, transcranial magnetic stimulation (TMS), vagus nerve stimulation (VNS) and deep brain stimulation (DBS). Some practitioners also include the administration of fast-acting pharmacological agents, such as ketamine, esketamine, and hallucinogens, within the purview of Interventional Psychiatry.

ECT is the biological treatment with the longest history of continuous use in psychiatry and remains the ''gold standard'' treatment of specific neuropsychiatric disorders (e.g., major depression, catatonia). The practice of ECT has been radically transformed by refinements in the nature of electrical stimulation, including adjustment of stimulus intensity to the individual patient's seizure threshold, abandonment of sine wave stimulation in favor or rectangular pulses, and the introduction of ultrabrief pulse stimulation. These innovations markedly reduced acute and long-term adverse cognitive effects. It is now also established that both the efficacy and cognitive effects of ECT are contingent on the current path and current density of the electrical stimulus.[2] This knowledge has prompted the development of the newest forms of ECT, focal electrically-administered seizure therapy and magnetic seizure therapy. These techniques offer improved spatial targeting of the seizure-inducing stimulus.[2]

TMS is a therapeutic intervention with multiple indications in psychiatry and neurology, including treatment-resistant depression (TRD), obsessive compulsive disorder, migraine, and smoking cessation. TMS induces current flow in neural tissue, largely as a function of proximity of the tissue to the magnetic coil producing the time-varying magnetic field. The major risk of TMS was thought to be seizure induction, but implementation of safety guidelines restricting stimulation parameters has made this a rare complication. Indeed, other than transient headache and scalp pain at the stimulation site, TMS is devoid of significant side effects. TMS was first approved by the US Federal Drug Administration for use in TRD, and its efficacy has been widely supported by randomized sham-controlled trials and large real-world, observational studies. Indeed, TMS appears at least as effective in TRD as any medication strategy tested in the Sequenced Treatment Alternative to Relieve Depression trial. Consequently, given its robust efficacy, favorable side effect profile, and lack of interaction with pharmacological agents, TMS is being reconsidered as a first-line treatment for major depressive episodes, including those among older adults.[3] A major practical impediment to TMS is that daily sessions over several weeks are typically required, and each session may last close to an hour. Recent innovations are also addressing this limitation. The use of theta burst stimulation, which involves a novel patterning of TMS pulses, can reduce session duration to a few minutes. Accelerated forms of TMS have also been developed in which multiple brief TMS sessions are given daily for several days. Initial evidence suggests that a few days of accelerated TMS can produce remission in a large percentage of severely ill TRD patients.[4]

Stimulation of the 10th cranial or vagus nerve can be accomplished noninvasively with transcutaneous electrical stimulation of sites in the ear or neck or by connecting a surgically implanted pulse generator to electrodes directly attached to the left cervical vagus nerve. The surgical form of VNS exerts clinically meaningful anticonvulsant effects and is widely used in the management of medication-resistant epilepsy. These anticonvulsant properties and observations of mood improvement in epilepsy patients treated with VNS prompted investigation in TRD. The antidepressant effects of VNS may take up to a year to fully manifest and are observed in about 40-50% of implanted patients. Critically, when clinical

Correspondence: Charles R. Conway, Department of Psychiatry, School of Medicine, Washington University, MSC 8134-17-04, 660 South Euclid Ave, Saint Louis, MO 63110, USA.
E-mail: conwaycr@wustl.edu
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improvement is obtained, the durability of benefit seems especially strong, a notable strength in a TRD population at high risk of relapse. However, despite receiving Federal Drug Administration approval for use in highly resistant TRD, defined as at least four failed adequate antidepressant trials, VNS in TRD never received coverage by medical insurers in the US, severely limiting access. Two large VNS trials in TRD are ongoing, one in Europe (RESTORE-LIFE)[5] and the other in the US (RECOVER).[6] In the RECOVER trial, up to 1,000 patients with unipolar and bipolar TRD are randomized to treatment with active or sham TMS for a period of one year, after which all patients receive active VNS for an additional four years.

DBS involves the delivery of electrical pulses to specific brain regions using electrical leads surgically implanted in specific nuclei or white matter tracts. DBS has become a routine procedure in the management of medication-resistant Parkinson's disease, dystonia, essential tremor, and epilepsy, and is under investigation in a variety of other conditions. DBS has also received Federal Drug Administration approval for compassionate use in obsessive compulsive disorder. Starting in the 1990s, DBS has been applied in TRD with targets including the subgenual cingulate (Brodmann's area 25), nucleus accumbens, ventral striatum, and the habenula.[7] Two recent sham-controlled DBS trials in TRD were stopped due to lack of short-term efficacy, but longer-term observations suggested that DBS may indeed exert durable antidepressant effects. Recent work has also emphasized the importance of identifying for each individual the white matter bundles or networks linked to proper lead placement.[8]

The neuromodulation technologies employed by Interventional Psychiatry are changing the nature of psychiatric treatment. ECT, VNS, and DBS are mainly intended for severely ill and treatment-resistant patients. In addition to TMS, newer innovations involving noninvasive, low intensity stimulation, such as trigeminal nerve stimulation or transcranial direct current stimulation, will likely have broader clinical applications, including home use. The technological goals of the field of neuromodulation include the development of novel methods to noninvasively deliver pharmacological agents to specific brain regions (focal pharmacology)[9] and to noninvasively stimulate deep brain regions without impacting surrounding tissue (noninvasive DBS).[10] These technologies, currently under development, typically rely on transcranial pulsed ultrasound. The therapeutic potentials of focal pharmacology and noninvasive DBS are extraordinary and will only deepen the revolution in psychiatric treatments already well under way.

Disclosure

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